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Receptive field structure of burst and tonic firing in feline lateral geniculate nucleus

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Abstract
There are two recognised modes of firing activity in thalamic cells, burst and tonic. A low-threshold (LT) burst (referred to from now on as 'burst') comprises a small number of high-frequency action potentials riding the peak of a LT Ca^{2+} spike which is preceded by a silent hyperpolarised state > 50 ms. This is traditionally viewed as a sleep-like phenomenon, with a shift to tonic mode at wake-up. However, bursts have also been seen in the wake state and may be a significant feature for full activation of recipient cortical cells. Here we show that for visual stimulation of anaesthetised cats, burst firing is restricted to a reduced area within the receptive field centre of lateral geniculate nucleus cells. Consistently, the receptive field size of all the recorded neurons decreased in size proportionally to the percentage of spikes in bursts *versus* tonic spikes, an effect that is further demonstrated with pharmacological manipulation. The role of this shrinkage may be distinct from that also seen in sleep-like states and we suggest that this is a mechanism that trades spatial resolution for security of information transfer.

Lateral geniculate nucleus (LGN) relay cells respond to afferent inputs in two very different modes: 'tonic' or 'burst' (Jahnsen & Llinas, 1984; reviewed by Sherman, 2001*a*). The predominance of burst or tonic spikes is directly related to the membrane potential of the cell, regulated by modulatory inputs to the nucleus. In depolarised conditions LGN cells fire in tonic or single spike mode; this is the predominant mode of response in the wake state, hence it has been traditionally associated with the transfer of information to the visual cortex. On the other hand, hyperpolarisation of the cell de-inactivates a low-threshold Ca^{2+} current (I_t) and promotes the appearance of spike bursts (Jahnsen & Llinas, 1984), consisting of a low-threshold (LT) Ca^{2+} spike crowned by a burst of action potentials; this type of response is common to sleep states and it has been associated with a failure to transfer visual information (Livingstone & Hubel, 1981; McCarley *et al.* 1983; McCormick & Feeser, 1990; Steriade *et al.* 1993; Steriade, 2000). However, recent evidence has shown not only that burst responses are also present during the wake state, in rodents, cats and monkeys, and even humans (Guido *et al.* 1992, 1995; Guido & Weyand 1995; Mukherjee & Kaplan, 1995; Radhakrishnan *et al.* 1999; Reinagel *et al.* 1999; Edeline *et al.* 2000; Ramcharan *et al.* 2000; Swadlow & Gusev, 2001; Weyand *et al.* 2001), but that they can also successfully relay visual information to the cerebral cortex (Guido *et al.* 1992, 1995; Sherman, 1996; Reinagel *et al.* 1999; Ramcharan *et al.* 2000; Weyand *et al.* 2001). An attractive, though highly debated theory (Sherman & Guillery, 1996; Sherman, 2001*a*,*b*; but see also Steriade, 2001), suggests that bursting could serve the initial detection of a stimulus. After this intense response, (the 'wake-up call') cells switch to tonic mode for a more meticulous analysis of the scene. In this schema, thalamic cells are continuously switching between tonic and burst under the influence of the modulatory inputs from brainstem and cortex. Despite the controversy, a still unanswered question is the relative contribution of burst *versus* tonic responses to the spatial structure of LGN receptive fields (RFs).

While the centre-surround antagonistic nature of the LGN RF might on the one hand spatially segregate spikes in bursts from tonic spikes by the operation of a simple thresholding effect, it is not clear in what way any such threshold might operate, since logically either high-frequency tonic or bursting spikes may be more effective at the border between centre and surround. A recent finding by Worgotter *et al.* (1998*b*) suggests that during states of synchronised EEG activity, the size of feline cortical receptive fields is larger than during desynchronised activity. Thus one intriguing possibility is that this may be the result of change in RF size in the input from thalamus.

In order to address this issue directly we recorded the visual responses of LGN relay cells extracellularly, mapping their RFs with sparse noise (see Methods). We differentiated spikes in bursts from tonic spikes and compared the spatial properties of the RFs. Our results show a 'shrinking' of the RF centre when constructed only with spikes in bursts, indicating that burst generation depends on the sub-position of the stimulus on the RF centre. Also, by pharmacologically manipulating the burst/tonic

ratio, we demonstrate, that the apparent RF size is dynamic and changes inversely with the percentage of burst spikes in a train.

Methods

All the experiments followed the regulations of the Spanish Physiology Society and the International Council for Laboratory Animal Science and European Union (statute no. 86/809). Briefly, adult cats (n= 6), 2.5–3.5 kg, were anaesthetised with halothane (1–5 % for induction, 0.1–0.5 % for maintenance) in nitrous oxide (70 %) and oxygen (30 %), and neuromuscular blockade was established with gallamine triethiodide (40 mg initial dose, then 10 mg $kg^{-1}h^{-1}$). EEG, ECG, expired CO_2 and temperature were monitored and maintained continuously to ensure that anaesthetic levels were altered as appropriate to maintain an adequate state of anaesthesia. Changes in parameters that indicated a decrease in anaesthetic levels (e.g. changes in intersystolic interval, decreasing spindle frequency, rise in end-tidal CO_2) were immediately counteracted by increasing halothane levels accordingly. Lidocaine (lignocaine) gel was applied to the ear bars of the stereotaxic frame and all wound margins were treated with subcutaneus injections of lidocaine. At the end of the experiments all of the animals were killed by anaesthetic overdose.

Recordings and visual stimulation

All observations were made in the LGN A laminae in an area ≤12 deg from the area centralis. The sample includes X and Y cells that were differentiated on the basis of a battery of standard tests, including the null test (linearity of spatial summation), RF size and eccentricity, type of response to flashing spots (transient or sustained) and presence or absence of shift effect. Relay cells have been differentiated from interneurons on the basis of the response to iontophoretic application of acetylcholine (ACh, McCormick & Prince 1987). All the cells reported here (n= 12) showed a robust increase in firing rate during ACh application, from which we conclude that our recordings were from relay cells. Multibarrelled pipettes and tungsten microelectrodes (FHC, USA) were used for extracellular recording and iontophoretic drug application. Waveforms and time-stamps were stored (Plexon Inc., USA) and offline spike sorting was used to assess adequate isolation of spikes. Pipettes were filled with NaCl (3 m) for recording and ACh (1 m, pH 5). All drugs were obtained from Sigma, Spain.

Visual stimuli were presented monocularly on a computer monitor (mean luminance of 14 cd m^{-1}, refresh rate 128 Hz). Receptive fields were mapped by forward correlation with sparse noise (Hirsch *et al.* 1998). Stimulus space was divided into a 20 × 20 grid (grid spacing ranged from 8 to 20 deg). In a given stimulus run, a series of black or white squares were flashed singly for a brief period of time (30 ms each with no inter-flash interval) at each location on the grid in pseudo-random order. The sequence was then repeated for the appropriate number of repetitions. The only restriction was that two consecutive stimuli could not be shown in contiguous locations. We chose such a mapping protocol because it is very successful at resolving the RF centres of thalamic cells; however, it is not very good at engaging the surrounds due to its small size and short duration. Other full-field stimuli that could have potentially been used to estimate thalamic RF dimensions (such as gratings) cause complex centre-surround interactions that would make the interpretation of the results more difficult. The RF, represented as a colour map, is obtained by averaging changes in activity (firing rate) that follow the presentation of the stimulus at each site on the grid. All maps were constructed from the responses to the stimulus polarity, which characterises the centre of the receptive field. Each map represents the accumulated response in each bin (spikes per bin) in a period of 25–50 ms after the stimulus onset. ‘Maps’ generated for other time windows showed no obvious spatial structure.

Spike train analysis

From a single spike train recorded during the sparse-noise protocol, we extracted the following event types.

Bursts. A burst consisted of at least three consecutive spikes with inter-spike intervals (ISI) less than 4 ms, preceded by a silent period of at least 50 ms. Other authors have used a similar method previously (Guido *et al.* 1992, 1995; Guido & Weyand, 1995; Reinagel *et al.* 1999; Weyand *et al.* 2001). However these authors used two spikes as the criteria for being considered as a burst whereas we used three spikes. The main risk of classifying spikes as burst or tonic using extracellular recordings is that high-frequency tonic spikes (HT burst, Guido *et al.* 1992; pseudo-burst, Swadlow & Gusev, 2001) can be considered as LT burst, in fact Lu *et al.* (1992) determined that up to 1.9 % of HT burst could be considered as LT burst

with this method. This small percentage becomes significant if we take into account that HT bursts represent a much larger fraction of the response than LT bursts. In our sample, most of our episodes of high frequency firing, or HT bursts, contain only two spikes (see also Swadlow & Gusev, 2001), hence we decided to consider a minimum of three spikes. With this strategy some LT burst was lost and considered as HT; however, in this case, because of the absolute number of spikes, a small percentage of LT burst is not appreciable when included into the HT burst.

Tonic spikes. All spikes that did not meet the criteria of spikes in bursts, as defined above.

Singleton burst. Isolated spikes that were preceded by a silent period of at least 50 ms and followed by a period greater than 10 ms during which no spike occurred.

Pseudo-bursts. At least two spikes with ISI less than 4 ms, preceded by another spike at an interval of less than 50 ms (also known as 'high-threshold bursts'Guido *et al.* 1992), a consequence of the increased firing rate induced by visual stimulation.

For more detailed analyses we further sorted pseudo-bursts with a preceding silent period of between 25 and 50 ms.

We routinely collected enough spike counts to allow the construction of receptive field maps with good signal-to-noise resolution for all event types extracted from the 'raw' spike train. Total data acquisition time ranged from 5 to 15 min.

Measurements of RF size. RF centres were fitted to two-dimensional Gaussian functions:

$$A\exp-((x-x_0)^2+(y-y_0)^2)/b\sigma^2,$$

where A is the value of the pixel that gave the maximum response; x_0 and y_0 are the co-ordinates of the maximum value; (in a small number of cases the data appeared to have more than one hotspot within the RF centre (i.e. firing equal to the maximum occurred in more than one pixel which were non-adjacent), in which case we smoothed the raw data by one pixel prior to fitting); σ is the s.d. of the 20 × 20 pixel array and b is varied to fit the envelope. The spatial RF used to adjust the Gaussian function was defined as all contiguous locations in the RF that were of the same sign as the strongest response and were larger than twice the s.d. of the baseline noise. Baseline was the mean value for all locations at a delay > 200 ms. Similar protocols have been used previously (Usrey *et al.* 1999, 2000).

Results

From a sample of 35 LGN cells, we were able to obtain sufficient spike numbers (in tonic and burst) to construct RF maps at high resolution for 22 cells. The average percentage of spikes occurring in bursts in these 22 cells was 11.30 ± 5.42 (mean ±s.e.m.). The sample included X (13) and Y (9), On (15) and Off (7) cells, and no significant differences between groups were evident.

Spikes in burst are restricted to hot spots in the RF centre

In 21 out of the 22 studied cells, the RF map obtained with spikes in bursts was smaller than the RF map obtained with all spikes or exclusively with tonic spikes. Figure 1 shows the RF maps from two LGN cells, labelled 'control' (all spikes, unsorted), and spikes separated into burst and tonic subclasses. In both cells, spatial collapse of the excitatory RF is evident during the burst condition when compared with total or tonic spikes alone. The observed effect is not a simple consequence of the reduction in the number of spikes in bursts, as shown in Fig. 1*B*, where the peak response was similar in burst and tonic modes.

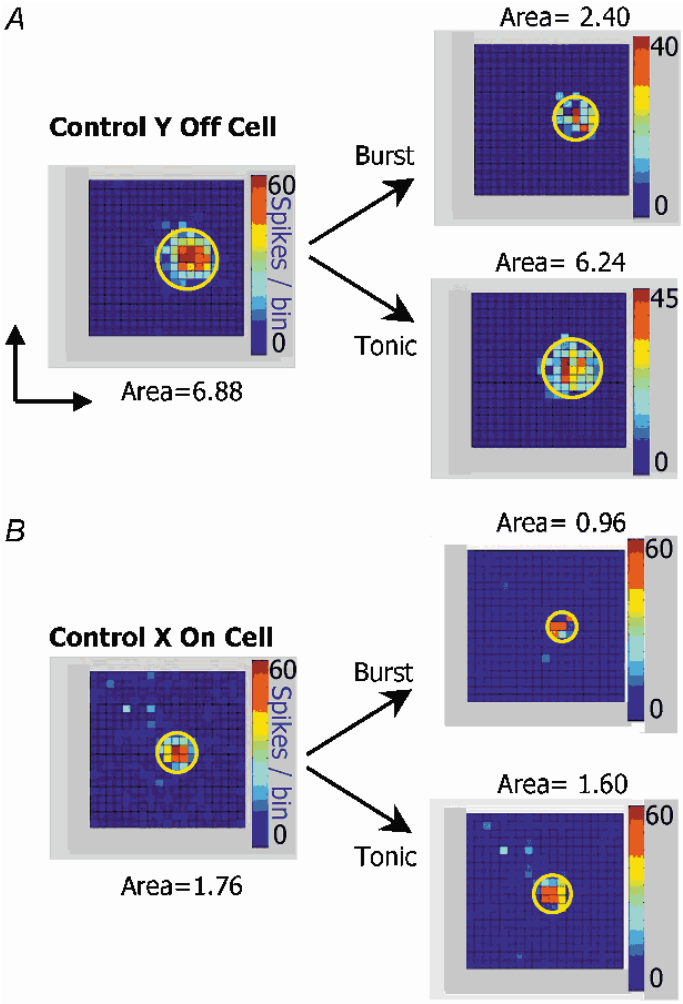

Figure 1 Spikes in burst are restricted to a central region of the receptive field
Receptive field maps for lateral geniculate nucleus (LGN) cells obtained by sparse noise stimulation. Firing rates are colour coded according to the scale to the right of the map. *A*, left, Y Off cell with a field obtained by counting all spikes for each pixel occurring in a temporal window of 25 ms beginning 25 ms after stimulus onset (stimuli were dark squares 0.4 deg × 0.4 deg on a light background). Map size is 8 deg × 8 deg, indicated by arrows. Right, the map divided into spikes occurring in bursts and spikes occurring in tonic mode. The receptive field (RF) area for the spikes in bursts is reduced by 66 % compared with control; tonic is not significantly different. *B*, left, control, all-spike map for an X On cell. Right, maps generated by sorting into bursts and tonic spikes, the burst field is 44 % smaller than the control.

Figure 2 summarises the results obtained for all 22 cells. Figure 2*A* is a scatter plot comparing the RF area in control *versus* the RF area obtained for those spikes in bursts (▪) or in tonic mode (^). It is clear that those spikes in bursts are restricted to a much smaller area, on average some 50 % smaller than either total spikes ($P < 0.001$ paired *t* test) or tonic alone ($P < 0.001$ *t* test), as illustrated in the histogram in Fig. 2*B*. No significant differences were detected between maps for all spikes and tonic spikes ($P = 0.89$). Both maps (burst and tonic) are centred at the peak of the RF constructed from the total number of spikes. As we explained in Methods, we decided to include as bursts, groups containing at least three spikes. However, we also analysed our sample to include bursts of only two spikes, and in 18 out of 22 cells the results were unaltered. Average values obtained applying this criterion are shown in Fig. 2*C*. The RF shrinks by 45 % using spikes in bursts when compared with all spikes ($P < 0.01$) and for tonic *versus* burst $P < 0.01$.

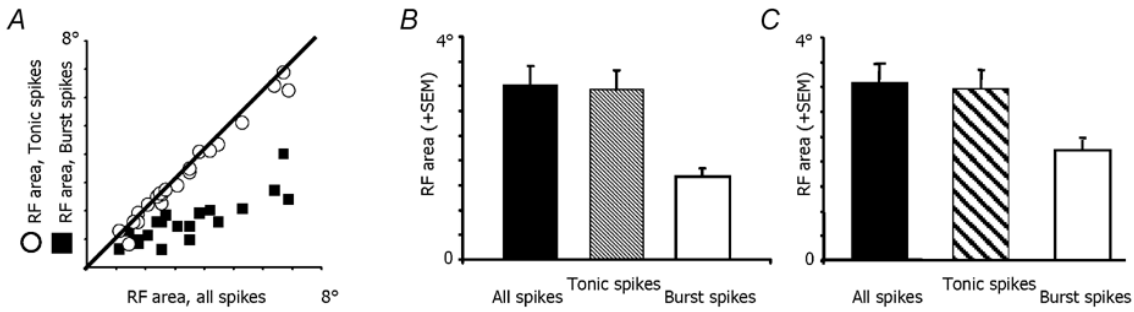

Figure 2 Receptive field area for spikes in burst is reduced when compared with other conditions
A, individual receptive field areas – mapped using all spikes (ordinate) compared with burst (▪) and tonic (^) spikes. *B*, histogram of mean values of the above series. On average the RF area measured using burst spikes is 52 % smaller than control; the size of the tonic mode field is unchanged. *C*, histogram of mean values counting two spikes (instead of three) as a burst.

Tonic and burst responses both occur throughout the time of RF mapping

It has been suggested that bursting acts as a mechanism for the detection of new stimuli (Sherman & Guillery, 1996; Sherman, 2001*a*,*b*). Bursts, therefore, should tend to be produced at the start of the visual response. This is true for gratings and for flashing spots (Guido *et al.* 1992; Weyand *et al.* 2001). Our data corroborate this, as is shown in the inset to Fig. 3. When the visual stimulus is a circular spot flashed on the RF for 300 ms, there is a transient response, followed by a sustained response that remains for the duration of stimulus presentation. When spikes in bursts are examined (red) it is clear that the spikes are concentrated in the transient response. The distribution of burst and tonic spikes during our sparse noise RF mapping protocol did not show such separation. Notice that because of the temporal structure of our stimulus, only the transient phase of the response is evoked. A representative example is shown in Fig. 3, showing the RF in control and the temporal development of the visual response for the three pixels underpinning the peak response. Spikes were separated into tonic (blue) and burst (red), clearly overlapping in time. A similar result was observed for all cells analysed (n= 10). However, this result almost certainly derives entirely from the temporal properties of the stimuli, which have a short time course (30 ms) precluding a more sustained response.

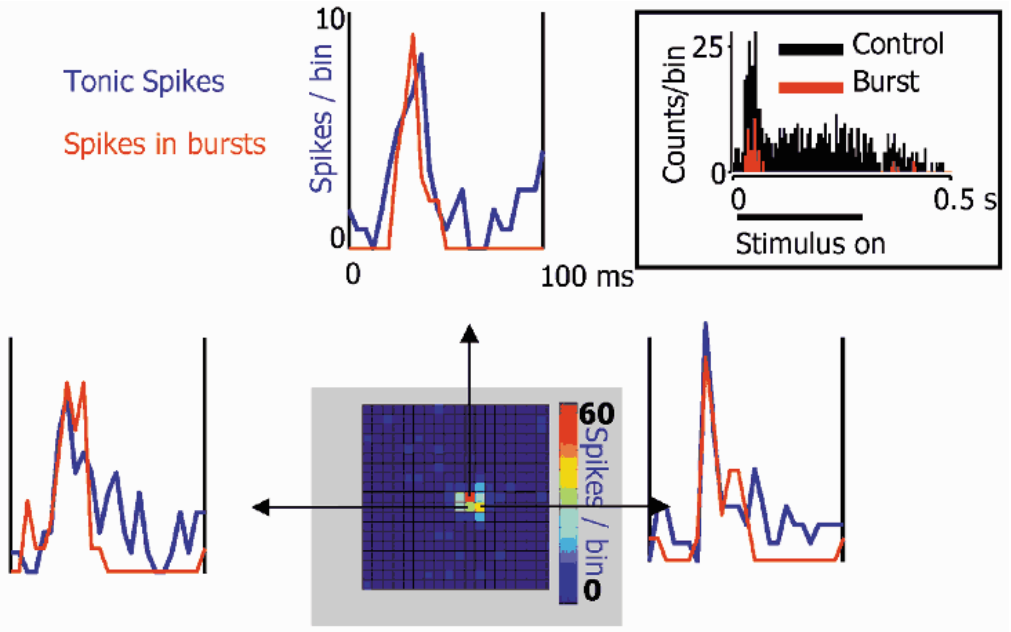

Figure 3 Temporal analysis of tonic and burst spikes
Centre, RF map produced by sparse noise. For each of the three central pixels the raw peristimulus time histograms (PSTH) are shown (indicated by arrows), separately for burst and tonic spikes. Inset, PSTH of the response of the same cell to a 300 ms flashed stimulus, showing all spikes (black) compared to burst spikes (red).

RF 'shrinkage' is only observed for LT bursts

There are two main properties that define a burst: a long (> 50 ms) silent period before the first spike of the burst and a short (< 4 ms) interspike interval between spikes that are part of the burst. In order to distinguish the influence of both aspects in our observed effect, we separately computed the RF for tonic, bursts, pseudo-bursts and singleton burst (see Methods). Figure 4*A* shows the results obtained for a Y ON cell. The RF area including all spikes is 4.5 deg^2, compared with only 2 deg^2 when computing only those spikes within bursts. This decrease was not observed when pseudo-bursts or singleton bursts were independently analysed, (4.1 deg^2 and 5.1 deg^2 respectively for this example). Analysis was restricted to cells with enough spikes in each category to compute maps, (*n*= 5): average values for all cells were 4.6 deg^2 for control, 3.2 deg^2 for pseudo-burst, 4.1 deg^2 for singleton burst and 2.1 deg^2 for genuine bursts.

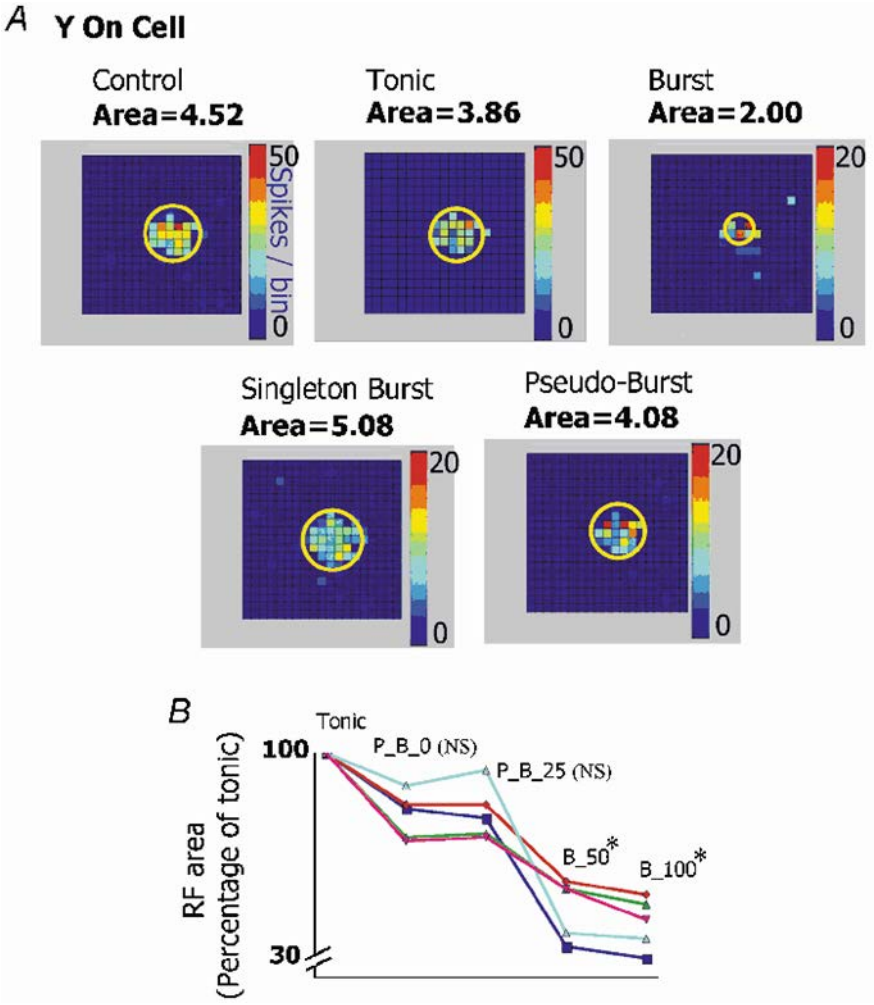

Figure 4 RF shrinkage only occurs with LT burst

A, RF maps for an On Y cell, created for control and following spike sorting into subgroups (see Methods). The RF area is only significantly reduced for genuine burst firing spikes. *B*, further analysis of 'burst' spikes, using different temporal criteria to define bursts, compared to RF area mapped using only tonic spikes from the same spike trains. P-B-0, pseudo-bursts with a preceding silence of < 25 ms; P-B-25, pseudo-bursts preceded by between 50 and 25 ms; B-50, LT bursts with a preceding silent period of > 50 ms; and B-100, LT bursts with a preceding silent period of 100 ms. The individual measures of RF are expressed as percentages of the RF size using tonic spikes alone, i.e. normalised. Consequently, the spread of tonic values is not shown, but statistically significant differences are marked by: NS, not significant; and **P* < 0.05. Data are from five individual cells.

The line graph in Fig. 4*B* shows the RF area for the five cells after further sorting. For all cells the RF size is larger for tonic spikes; while there appears to be a slight reduction in area for pseudo-bursts with a preceding silence <25 ms (P-B-0,) and pseudo-bursts preceded by between 50 and 25 ms (P-B-25,) these decreases fail to reach significance (*P*= 0.44 and *P*= 0.60, respectively, *t* test). The reduction in RF size occurs when the preceding silent period is >50 ms (LT burst, B-50, *P* < 0.05) and the RF area did not

significantly decrease further when it is increased to 100 ms (B-100, see Methods), supporting our use of the liberal method to characterise burst firing.

Apparent RF size is dependent on the percentage of spikes in bursts

The results show that the RF centre shrinks when spikes in bursts are extracted from a given spike train. This predicts that an increase in the percentage of spikes in a train that are in bursts should decrease the RF size, as measured over the entire train. In six cells we mapped the RF in normal conditions and then remapped it after artificially increasing the percentage of spikes occurring in bursts by increasing the anaesthetic level. In Fig. 5 (top) we show the RFs obtained using all spikes, burst and tonic spikes in the normal anaesthesia condition. As shown in Fig. 1, the RF shrinks using only spikes in bursts compared to all or tonic spikes. This state of anaesthesia (halothane 0.5 %), typically used in visual neuroscience experiments, is characterised by a relatively low-amplitude EEG exhibiting occasional sleep spindles, as observed in the sample shown above the maps. In this state, for this particular cell, 23 % of spikes in the train were classified as burst. After increasing the level of anaesthesia (halothane 1.5 %), the percentage of spikes in bursts was 46 % of the total. The effect of such a depth of anaesthesia was clearly visible in the EEG, heavily dominated by slow activity, as well as in other parameters (e.g. reduction in cardiac rate, etc.). RF maps obtained under these conditions are presented in Fig. 5 (bottom). Firstly, increasing the percentage of spikes in bursts reduces RF area (2.4 *versus* 3.6 deg^2 in normal anaesthesia). Secondly, under deepened anaesthesia the burst RF was similar in area and location to that obtained with tonic spikes (2.1 *versus* 2.2 deg^2) indicating that at this level both tonic and burst spikes are restricted to the same hot spot. Also, burst RF maps in normal and deepened anaesthesia conditions are essentially identical. The results were similar for all six studied cells; on average during deepened anaesthesia, tonic RF size was 2.4 *versus* 2.2 deg^2 for burst RF.

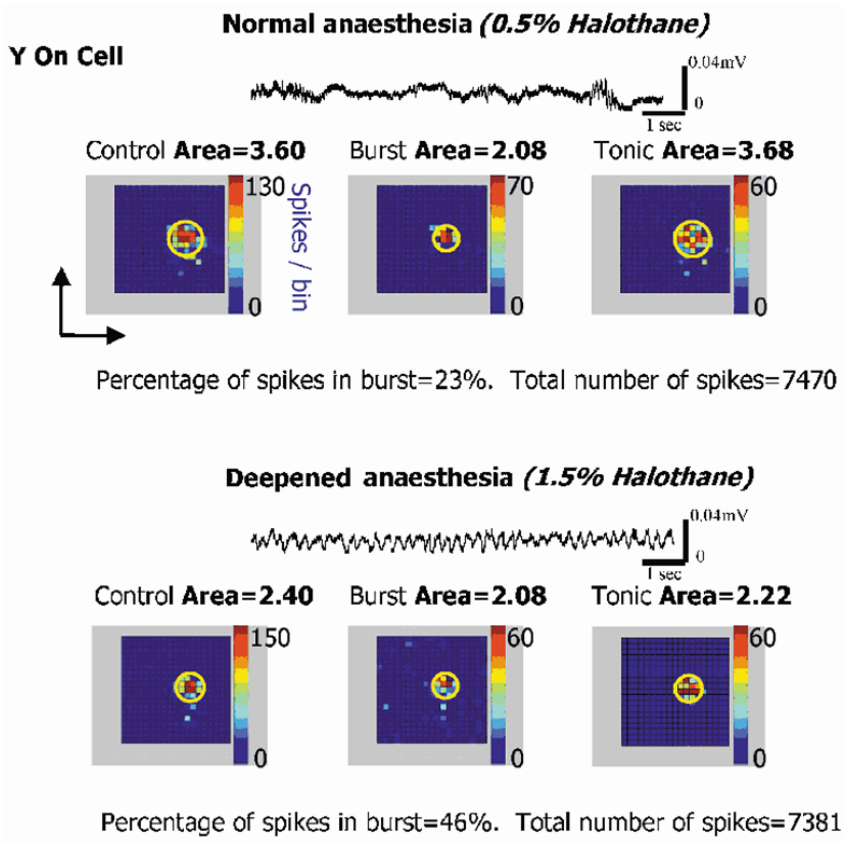

Figure 5 *Effect of increased anaesthesia on RF area*
Top, RF maps obtained under a standard anaesthetic protocol of 0.5 % halothane, again showing a mapping area of 8 × 8 deg (arrows), firstly using all spikes, then burst and tonic modes separately. A representative 10 s segment of EEG recorded concurrently is shown above the maps. Lower, RF maps from the same cell, now during an increased level of anaesthesia (halothane 1.5 %). Again, a segment of EEG is shown above the maps. Total number of spikes recorded was similar for the two conditions; however, increased anaesthesia increased the proportion of spikes occurring in bursts from 23 % to 46 %.

In order to understand this mechanism better, after increasing the number of spikes in burst with anaesthesia, we applied ACh locally. This is an excitatory neurotransmitter in the thalamus that is known to switch relay cells firing from burst to tonic mode (McCormick & Prince, 1987; Francesconi *et al.* 1988). Figure 6*A* (left) shows the RF obtained with all spikes during normal anaesthesia, and, as in Fig. 5, RF shrinks during increased level of anaesthesia, (centre). Then, still in the deepened anaesthetic state, iontophoretic ejection of ACh (n= 6) significantly decreased the percentage of spikes in burst ($P < 0.001$) and increased the RF size ($P < 0.01$), Fig. 6*B*. Notice that the RF size during ACh is even larger than that obtained during normal anaesthesia. Interestingly, increased application levels of ACh can further increase firing rates, but without further increasing RF area.

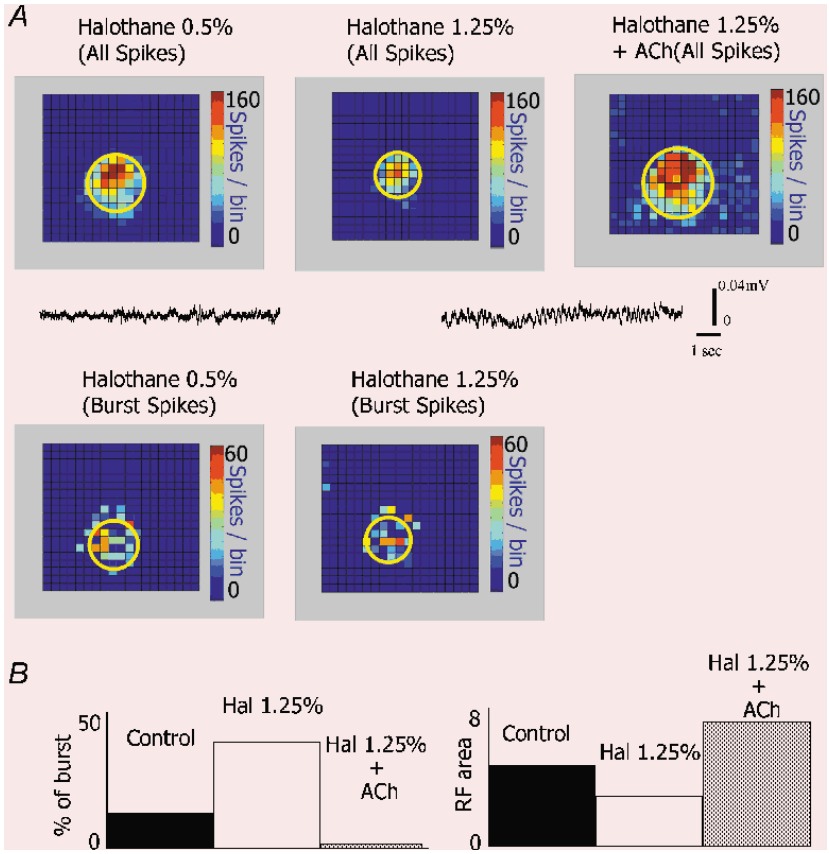

Figure 6 Effect of ACh on RF size
A, RF maps of a Y On cell obtained from the entire spike train recorded in response to our sparse-noise stimulus under standard anaesthesia, increased levels of anaesthesia and a combination of increased anaesthesia and local application of Ach (upper row); and RFs obtained counting only spikes in burst in different conditions (lower row). Two segments of EEG data are shown below, under normal anaesthesia and increased anaesthesia. Local application of ACh did not alter the EEG. *B*, level of burst firing (left) and RF area (right) under the conditions listed in *A* for the six cells studied. Note that even in the presence of ACh, some spikes are still produced in burst (in this particular case, approximately 3 % of all spikes in the train were contained in bursts).

Discussion

The role of the thalamus in sensory processing is still widely debated. Possible functions range from a mere relay station to a significant role in consciousness and attention (Portas *et al.* 1998). The controversy arises because thalamic relay neurons fire in two different modes: tonic and burst. Burst mode has been shown to be predominant during sleep states and only 'residual' while awake (Livingstone & Hubel, 1981; McCarley *et al.* 1983; Steriade *et al.* 1993; Swadlow & Gusev, 2001; Weyand *et al.* 2001). Hence, burst mode has been traditionally accepted as a non-transmission state (Livingstone & Hubel, 1981; McCarley *et al.* 1983; McCormick & Feeser, 1990; Steriade, 2000). On the other hand, evidence points to bursting as a different mode of sensory transmission (Guido *et al.* 1995; Guido & Weyand, 1995; Sherman, 1996; Sherman & Guillery, 1996; Sherman, 2001*a*) postulating that bursts can have a fundamental role in stimulus detection – a 'wake up call'.

Here we demonstrate that bursts are evoked only when the stimulus falls on hot spots in the RF centre and that RF size changes inversely with percentage of spikes in bursts. It is important to emphasise that we have extracted burst and tonic spikes offline from a single spike train in response to a visual stimulus – bursts are seen throughout the spike train, not clumped or gathered in any particular time region. This result is initially surprising because it has been recently demonstrated that in the visual cortex, receptive fields expand during synchronised EEG states (Worgotter *et al.* 1998). These authors proposed that this effect is the result of restructuring the temporal pattern of thalamocortical activity, thereby suggesting that the same effect might be found in the thalamus. However, our results show that the thalamic RFs shrink, rather than expand, when examined during burst firing *versus* tonic firing, suggesting that the mechanism for cortical expansion will probably be found in the cortex itself. We believe our results can easily be integrated into the 'wake up call' theory. Firstly, we should examine the nature of the spatial shrinking of the RF under these conditions. We would not wish to suggest that, somehow, the LGN has shifted to a different level of spatial analysis; such spatial shrinking may operate at cortical levels to enhance selectivity (Worgotter *et al.* 1998) but in the LGN the shrinkage of the RF is the result, we believe, of a mechanism designed to ensure accurate transmission of the presence of novel stimuli and eliminate possible false positive reporting. Spatial information is not lost, since burst firing only occurs at the beginning of the spike train, after which the cell fires in tonic mode, and the full RF spatial information becomes available to cortex. In this scenario, the apparent loss of detection in the now unresponsive regions of the RF centre will be covered by other LGN cells with partially overlapping RFs. Actually, this could represent a mechanism to precisely localise the stimulus in the visual space immediately because it reduces the area from where a cell becomes active and hence reduces the number of cells sending information to the visual cortex.

Secondly, it has been argued that bursts cannot play a prominent role in visual processing because they represent less than 1 % of spikes during awareness (Steriade, 2001, but see Ramcharan *et al.* 2000; burst is common during visual stimulation, ≈10 % of the time in monkeys). However, for the role we propose the actual number is not critical, since a single burst signalling the appearance of a new stimulus could be enough to activate the shift to tonic mode (Sherman, 2001*a*). Indeed, individual cells are known to shift between tonic and burst mode even in the absence of stimulation (Reinagel *et al.* 1999; Weyand *et al.* 2001) and in our experiments we did not find any pattern of continuous burst periods or absences; commonly, bursts were mixed with tonic spikes throughout the recording session (Reinagel *et al.* 1999). This shift between burst and tonic modes may be in response to intrinsic membrane properties coupled with non-retinal inputs, e.g. brainstem and cortex, which comprise up to 90 % of input to LGN cells (Erisir *et al.* 1997). Thus, a simple stochastic distribution of cells shifting in and out of burst, across the LGN 'map' of space, could act as an extremely effective novelty detecting system.

An obvious explanation of the effect we have observed is that of an 'iceberg effect'– the incoming retinal spike train is only sufficiently potent in its central region to lift the thalamic cell out of a hyperpolarised state, and simply as a consequence of the Gaussian envelope of the retinal RF, we see bursting spikes only within a central region of the LGN RF. This seems likely to be the mechanism for bursts evoked during sleep-like states. In our anaesthetised cat, and more importantly in a wake state, it remains possible that some novel mechanism is used, which cannot easily be identified by our extracellular recording technique. We believe that our analysis of RF size using pseudo-bursts argues at least in part against a simple 'iceberg effect'. Pseudo-bursts include spikes with interspike intervals similar to those observed in bursts (see Methods), hence eliciting pseudo-bursts is also likely to require a strong input (they were originally called 'high-threshold bursts' by Guido *et al.* 1992). If the observed effect was a consequence of a stronger input, and those stronger inputs are limited to the central area of the RF centre, where the maximum response is achieved, the RF shrinking effect should be visible also for pseudo-bursts. However, pseudo-bursts are widely distributed over the RF. This suggests that LT bursts may have some property, other than a high threshold, that restricts them to the described region.

In reality, even though the mechanism by which bursting is achieved in the wake state may indeed be similar to the bursting seen in sleep and due simply to an iceberg effect, the consequences are significantly different in the two scenarios – during sleep, hyperpolarisation is achieved by the widespread withdrawal of major modulatory brainstem influences and corticofugal feedback. In the wake state, both of these pathways are active, and it therefore seems more likely that if hyperpolarisation drives the bursting responses, it will be actively produced in response to a visually driven inhibitory process (for example, cortically driven LGN 'length' tuning, see Murphy & Sillito, 1987). Whether retinal or cortical in origin, this hyperpolarisation involves only restricted areas of the visual space, unlike that driven by the diffuse connections from the brainstem that, when activated, tend to engage the LGN as a whole.

We have suggested that a burst may trigger a subsequent shift to tonic mode – why then have a burst in the first place? We should not forget that bursts, because of their temporal properties, ensure a higher efficacy in the transmission to a postsynaptic target, the layer 4 simple cell; the efficacy of the first spike

is increased by 200 %, due to the quiescent preceding period (Swadlow & Gusev, 2001). Because of the relatively high tonic background firing rate of LGN cells, bursts are the most likely temporal sequence to include this period. Also, the short ISI within bursts are thought to increase the efficacy of the subsequent spikes in the burst – it has been proposed that an ISI of less than 10 ms duration increases the efficacy of the thalamo-cortical connection (Usrey *et al.* 1999). Bursts are much more likely to activate cortical cells than tonic mode spikes alone, which may often fail to elicit appropriate cortical spiking. Following activation by bursts, it is likely that a cascade of events is initiated, including feedback information from cortex, for example shifting the firing pattern directly into tonic mode (McCormick & von Krosigk, 1992), inducing synchrony between LGN cells (Sillito *et al.* 1994) and/or changing the temporal pattern of their responses (Worgotter *et al.* 1998*a*). Furthermore, Beierlein *et al.* (2002) have shown that high-frequency thalamo-cortical inputs triggered widespread recurrent activity in populations of neurons in layer 4 and then spread into adjacent layers 2/3 and 5; hence, burst could be an optimal input to fully activate cortical circuits. In our hands, it is unlikely that the mapping protocol we have adopted will reveal a significant cortico-fugal role in the structure of the observed RF (Rivadulla *et al.* 2002). Although sparse noise can adequately map (i.e. stimulate) layer 6 RFs (Hirsch *et al.* 1998), the temporal dynamics of the feedback pathway are considered to be too slow to contribute to our LGN responses (Harvey, 1978, 1980; Grieve & Sillito, 1995).

As predicted, increased halothane levels induced a deep sleep-like synchronised EEG, reduced the discharge rate of LGN cells and increased the relative numbers of spikes occurring in burst (Guido & Weyand, 1995; Reinagel *et al.* 1999), and decreased the RF size, in a manner similar to that previously shown in the auditory and somatosensory system (Friedberg *et al.* 1999; Edeline *et al.* 2000). During deep anaesthesia we are probably underestimating the percentage of bursting spikes; the general reduction in excitability probably decreases the number of spikes per burst, and therefore a number of the events counted as single spikes could be bursts of one or two spikes. This could explain the equal size of the RF for spikes in burst and tonic spikes in this condition. Interestingly, the asymptotic nature of the RF size seen during local application of ACh seems to define the maximal extent of the excitatory retinal input, yet it is pertinent to note that even at the highest levels of firing, some burst responses were still seen.

In summary, we suggest that the data reported here, while recognising the role of burst firing in sleep and the sleep-to-wake transition, support a mechanistically different role for the burst firing in the LGN in the wake state as a trigger for detection of novel stimuli of potential interest and location of the stimulus in the visual field.

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References

Beierlein M, Fall CP, Rinzel J & Yuste R (2002). Thalamocortical bursts trigger recurrent activity in neocortical networks: layer 4 as a frequency-dependent gate. J Neurosci 15, 9885–9894.

Edeline JM, Manunta Y & Hennevin E (2000). Auditory thalamus neurons during sleep: changes in frequency selectivity, threshold, and receptive field size. J Neurophysiol 84, 934–952.

Erisir A, Van Horn SC & Sherman SM (1997). Relative numbers of cortical and brainstem inputs to the lateral geniculate nucleus. Proc Natl Acad Sci U S A 94, 1517–1520.

Francesconi W, Muller CM & Singer W (1988). Cholinergic mechanisms in the reticular control of transmission in the cat lateral geniculate nucleus. J Neurophysiol 59, 1690–1718.

Friedberg MH, Lee SM & Ebner FF (1999). Modulation of receptive field properties of thalamic somatosensory neurons by the depth of anesthesia. J Neurophysiol 81, 2243–2252.

Grieve KL, & Sillito AM (1995). Differential properties of cells in the feline primary visual cortex providing the corticofugal feedback to the lateral geniculate nucleus and visual claustrum. J Neurosci 15, 4868–4874.

Guido W, Lu SM & Sherman SM (1992). Relative contributions of burst and tonic responses to the receptive field properties of lateral geniculate neurons in the cat. J Neurophysiol 68, 2199–2211.

Guido W, Lu SM, Vaughan JW, Godwin DW & Sherman SM (1995). Receiver operating characteristic (ROC) analysis of neurons in the cat's lateral geniculate nucleus during tonic and burst response mode. Vis Neurosci 12, 723–741.

Guido W, & Weyand T (1995). Burst responses in thalamic relay cells of the awake behaving cat. J Neurophysiol 74, 1782–1786.

Harvey AR, (1978). Characteristics of corticothalamic neurons in area 17 of the cat. Neurosci Lett 7, 177–181.

Harvey AR, (1980). A physiological analysis of subcortical and commissural projections of areas 17 and 18 of the cat. J Physiol 302, 507–534.

Hirsch JA, Alonso JM, Reid RC & Martinez LM (1998). Synaptic integration in striate cortical simple cells. J Neurosci 18, 9517–9528.
Jahnsen H, & Llinas R (1984). Electrophysiological properties of guinea pig thalamic neurones: an in vitro study. J Physiol 349, 205–226.
Livingstone MS, & Hubel DH (1981). Effects of sleep and arousal on the processing of visual information in the cat. Nature 291, 554–561.
Lu SM, Guido W & Sherman SM (1992). Effects of membrane voltage on receptive field properties of lateral geniculate neurons in the cat: contributions of the low-threshold Ca^{2+} conductance. J Neurophysiol 68, 2185–2198.
McCarley RW, Benoit O & Barrionuevo G (1983). Lateral geniculate nucleus unitary discharge in sleep and waking: state- and rate-specific aspects. J Neurophysiol 50, 798–818.
McCormick DA, & Feeser HR (1990). Functional implications of burst firing and single spike activity in lateral geniculate relay neurons. Neuroscience 39, 103–113.
McCormick DA, & Prince DA (1987). Actions of acetylcholine in the guinea-pig and cat medial and lateral geniculate nuclei, in vitro. J Physiol 392, 147–165.
McCormick DA, & von Krosigk M (1992). Corticothalamic activation modulates thalamic firing through glutamate 'metabotropic' receptors. Proc Natl Acad Sci U S A 89, 2774–2778.
Mukherjee P, & Kaplan E (1995). Dynamics of neurons in the cat lateral geniculate nucleus: in vivo electrophysiology and computational modeling. J Neurophysiol 74, 1222–1243.
Murphy PC, & Sillito AM (1987). Corticofugal feedback influences the generation of length tuning in the visual pathway. Nature 329, 727–729.
Portas CM, Rees G, Howseman AM, Josephs O, Turner R & Frith CD (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. J Neurosci 18, 8979–8989.
Radhakrishnan V, Tsoukatos J, Davis KD, Tasker RR, Lozano AM & Dostrovsky JO (1999). A comparison of the burst activity of lateral thalamic neurons in chronic pain and non-pain patients. Pain 80, 567–575.
Ramcharan EJ, Gnadt JW & Sherman SM (2000). Burst and tonic firing in thalamic cells of unanesthetized, behaving monkeys. Vis Neurosci 17, 55–62.
Reinagel P, Godwin D, Sherman SM & Koch C (1999). Encoding of visual information by LGN bursts. J Neurophysiol 81, 2558–2569.
Rivadulla C, Martinez LM, Varela C & Cudeiro J (2002). Completing the corticofugal loop: a visual role for the corticogeniculate type 1 metabotropic glutamate receptor. J Neurosci 22, 2956–2962.
Sherman SM, (1996). Dual response modes in lateral geniculate neurons: mechanisms and functions. Vis Neurosci 13, 205–213.
Sherman SM, (2001a). Tonic and burst firing: dual modes of thalamocortical relay. Trends Neurosci 24, 122–126.
Sherman SM, (2001b). A wake-up call from the thalamus. Nat Neurosci 4, 344–346.
Sherman SM, & Guillery RW (1996). Functional organization of thalamocortical relays. J Neurophysiol 76, 1367–1395.
Sillito AM, Jones HE, Gerstein GL & West DC (1994). Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. Nature 369, 479–482.
Steriade M, (2000). Corticothalamic resonance, states of vigilance and mentation. Neuroscience 101, 243–276.
Steriade M, (2001). To burst, or rather, not to burst. Nat Neurosci 4, 671.
Steriade M, McCormick DA & Sejnowski TJ (1993). Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679–685.
Swadlow HA, & Gusev AG (2001). The impact of 'bursting' thalamic impulses at a neocortical synapse. Nat Neurosci 4, 402–408.
Usrey WM, Alonso JM & Reid RC (2000). Synaptic interactions between thalamic inputs to simple cells in cat visual cortex. J Neurosci 20, 5461–5467.
Usrey WM, Reppas JB & Reid RC (1999). Specificity and strength of retinogeniculate connections. J Neurophysiol 82, 3527–3540.

Weyand TG, Boudreaux M & Guido W (2001). Burst and tonic response modes in thalamic neurons during sleep and wakefulness. J Neurophysiol 85, 1107–1118.
Worgotter F, Nelle E, Li B & Funke K (1998a). The influence of corticofugal feedback on the temporal structure of visual responses of cat thalamic relay cells. J Physiol 15, 797–815.
Worgotter F, Suder K, Zhao Y, Kerscher N, Eysel UT & Funke K (1998b). State-dependent receptive-field restructuring in the visual cortex. Nature 396, 165–168.